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Cancer 2017 Nov 15; 123:4488

High Rates of Marijuana Use in Cancer Patients

In a state with legalized marijuana, 24% of patients had used marijuana in the last year, primarily for pain, nausea, stress, anxiety, and depression.

Medicinal use of marijuana is increasingly common in the U.S. despite limited evidence of efficacy and ambiguous boundaries between medicinal and recreational use ([NEJM JW Psychiatry Feb 2017](#) and [JAMA2017; 317:209](#)). In this survey-based study, researchers examined use in outpatients from a Seattle cancer center after state legalization of marijuana.

Of 2737 patients approached, 926 responded (34%; median age, 58; >50% college-educated; 66% with solid tumors). About 66% had a history of lifetime marijuana use, and 24% were “active users.” Although 74% would have preferred to learn about marijuana from their cancer team, most got their information elsewhere (e.g., friends, websites, or other patients).



Among active users, two thirds used marijuana before cancer diagnosis. Three quarters consumed weekly; over half consumed daily. Intake was by inhalation, edibles, or both. Almost two thirds had told their physicians about their marijuana use. They used marijuana largely to treat pain, nausea, and appetite (75%) or cope with stress, anxiety, and depression (63%). About 26% said they used it to help treat their cancer.

COMMENT: The rate of marijuana use was surprisingly high in this group of cancer patients; the findings suggest that clinicians should routinely ask our patients with chronic illness about marijuana use. Much of the use seems to be driven by neuropsychiatric distress arising naturally from the burden of illness; stress and anxiety also powerfully affect pain and nausea/appetite. Ease of access to legalized marijuana may have facilitated marijuana use. Whether these patients pursued established treatments for neuropsychiatric distress, or did not because of their marijuana use, is unknown.

CITATION(S): Pergam SA et al. Cannabis use among patients at a comprehensive cancer center in a state with legalized medicinal and recreational use. *Cancer* 2017 Nov 15; 123:4488.
(<http://dx.doi.org/10.1002/cncr.30879>)

Gastroenterology 2018 Jun 29

Methotrexate Is Ineffective for Long-Term Maintenance in Ulcerative Colitis

In the latest trial, methotrexate shows no improvement over placebo for maintaining remission.

Methotrexate has been shown to be effective in treating Crohn disease, but its use in ulcerative colitis has not been as successful. In a multicenter, 48-week trial, subcutaneous methotrexate (25 mg once/week) was given first as open-label therapy for induction of remission in 179 patients with moderately active ulcerative colitis and nonresponse to other therapies, including biologics. Fifty-one percent of patients achieved response at week 16, and 84 patients entered a randomized, placebo-controlled, 32-week maintenance period. The proportion of patients in steroid-free remission at the end of the study period was no greater in the group receiving methotrexate compared with the placebo group (27% and 30%, respectively).

COMMENT: Treatment options for active ulcerative colitis include thiopurines and biologics, but these drugs are expensive and come with significant adverse side effects. Previous studies of methotrexate that showed efficacy were uncontrolled, and a previous randomized trial done in France did show higher clinical remission rates with methotrexate versus placebo, but there was no maintenance phase to the study. Twenty percent of patients experienced nausea in this study, and methotrexate is not a good option for those who are contemplating pregnancy or have risk factors for liver disease. It is cheap, however, and perhaps its appropriate role is to help with induction of active disease and provide a bridge to another agent for maintenance therapy.

CITATION(S): Herfarth H et al. Methotrexate is not superior to placebo in maintaining steroid-free response or remission in ulcerative colitis. *Gastroenterology* 2018 Jun 29; [e-pub].
(<https://doi.org/10.1053/j.gastro.2018.06.046>)



JAMA 2017 Dec 12; 318:2190

Thyroid Autoimmunity and Assisted Pregnancy: Levothyroxine May Not Be the Solution

In a Chinese trial, levothyroxine had no effect on miscarriage rates after IVF in women with antithyropoxidase antibodies and normal thyroid function.

Thyroid autoimmunity is the most common cause of hypothyroidism in women of childbearing age; moreover, this immune condition is associated with excess risks for infertility, miscarriage, and preterm labor. To explore the pregnancy-associated outcomes of giving levothyroxine during a single cycle of in vitro fertilization (IVF) to women with antithyropoxidase antibodies and normal thyroid function, investigators in China conducted an open-label trial involving 600 women (mean age, 32) who were randomized to levothyroxine or no treatment within 2 to 4 weeks before beginning an IVF cycle. Levothyroxine dosages were sufficient to maintain thyroid-stimulating hormone (TSH) levels within the normal range for pregnancy but without rendering TSH unmeasurable.

Throughout the 4.5-year study, miscarriage rates (defined as pregnancy ending before 28 weeks' gestation) were 10.3% (11 of 107) in the levothyroxine group and 10.6% (12 of 113) in the control group. Almost all miscarriages occurred during the first 12 weeks of gestation. Rates of clinical pregnancy, live birth, and preterm delivery did not differ between groups.

COMMENT: Management of thyroid abnormalities during pregnancy remains challenging and controversial, but these findings add to our knowledge: If thyroid function is normal, levothyroxine administration to women with antithyropoxidase antibodies does not improve either pregnancy rates (during IVF) or pregnancy outcomes. As other studies indicate, even treatment of women in general with subclinical hypothyroidism (elevated TSH with normal T4) must be considered carefully because of the potential risks inherent in the therapy itself (NEJM JW Womens Health Mar 2017 and BMJ 2017; 356:i6865).

CITATION(S): Wang H et al. Effect of levothyroxine on miscarriage among women with normal thyroid function and thyroid autoimmunity undergoing in vitro fertilization and embryo transfer: A randomized clinical trial. JAMA 2017 Dec 12; 318:2190. (<http://dx.doi.org/10.1001/jama.2017.18249>)

Pediatrics 2018 Jan

Earlier Menarche Is Associated with Depression and Antisocial Behavior in Adulthood

Longitudinal data show persistence of these associations into women's late 20s and early 30s.



To determine if girls who enter puberty earlier than their peers — a risk factor for numerous mental health problems during adolescence — continue to have excess risk for those problems during young adulthood, investigators analyzed data on 7800 girls from a national longitudinal study in the U.S. Girls were followed up at four time points (mean ages at enrollment and final follow-up were 15 and 28 years, respectively), and reported their age at menarche and how often in the past 12 months they engaged in various antisocial behaviors (e.g., property damage, stealing). Participants also completed a depression assessment tool.

Consistent with other studies, earlier menarche was associated with increased risk for depression during adolescence, and also in adulthood. Further analyses (controlling for other factors such as race/ethnicity, absence of father, etc.) showed that the increased risk in adulthood was primarily due to persistence of adolescent depression. Earlier menarche was also associated with increased levels of antisocial behavior during adolescence and young adulthood; further analyses indicated persistence of the behaviors to adulthood and some slight worsening in adulthood as well.

COMMENT: Because these results indicate that risks for depressive symptoms and antisocial behaviors associated with early menarche persist well into adulthood, prevention is key. Anticipatory guidance in pediatrics is generally age based, but for adolescent girls who mature early, focusing on their age and ignoring their physical development may well result in missing a critical window for intervention. Pediatricians can counsel parents that their early-maturing daughters (particularly those maturing much earlier than peers) will need extra support and supervision, as their cognitive development may lag behind their pubertal development, leaving them ill-equipped to negotiate being treated as older by peers and adults.

CITATION(S): Mendle J et al. Age at menarche, depression, and antisocial behavior in adulthood. *Pediatrics* 2018 Jan; 141:e20171703. (<https://doi.org/10.1542/peds.2017-1703>)

JAMA 2017 Dec 19; 318:2317

Pessary Placement for Preventing Preterm Birth: The Ring Lives to See Another Day

Randomized controlled trial demonstrates benefit of the cervical pessary for short cervix.

Preterm birth has proven elusive to prevent, with few clearly efficacious evidence-based interventions. Use of a cervical pessary in the setting of short cervix has been studied in several trials with mixed results; and a meta-analysis showing no benefit effectively nullified this inexpensive intervention. Now, Italian investigators have conducted another randomized trial of pessary use versus nonuse (control) in 300 asymptomatic women with cervical lengths <25 mm and no prior preterm births. All participants with cervical lengths <20 mm received vaginal progesterone regardless of group assignment.

Mean cervical length at study entry was 12 mm. Compared with the women in the control group, those who received pessaries were less likely to experience spontaneous preterm birth at <34 weeks' gestation (7% vs. 15%; $P=0.04$). Newly occurring vaginal discharge was more common in the pessary group.

COMMENT: Despite earlier evidence to the contrary, this trial suggests a benefit of pessary placement in the setting of short cervix. Discrepancy between these and other results may be explained by differences in patient populations, pessary placement techniques, and use of adjunctive therapies. Although the mixed data call for caution against fully jumping back on the pessary bandwagon, I have found this to be a well-tolerated, apparently low-risk intervention for women at risk for preterm delivery. Thus, I will continue to offer it to selected patients — particularly those with very short cervix despite use of vaginal progesterone.

CITATION(S): Saccone G et al. Effect of cervical pessary on spontaneous preterm birth in women with singleton pregnancies and short cervical length: A randomized clinical trial. JAMA 2017 Dec 19; 318:2317. (<http://dx.doi.org/10.1001/jama.2017.18956>)

Silver RM and Branch DW. Cervical pessary to prevent preterm birth. JAMA 2017 Dec 19; 318:2299. (<http://dx.doi.org/10.1001/jama.2017.18955>)

J Antimicrob Chemother 2018 May 16

Bezlotoxumab for *C. difficile* Colitis — Is Timing Critical?

Efficacy of bezlotoxumab given during the treatment course for C. difficile colitis was independent of timing of administration.

C. difficile infection (CDI), the most frequent cause of healthcare-associated gastrointestinal infection in the U.S., often takes a recurrent and complicated course in patients with comorbidities. Bezlotoxumab, a recently FDA-approved monoclonal antibody directed against *C. difficile* toxin B, reduces recurrence in high-risk patients by ≈40% when given together with antibiotic treatment for CDI (see NEJM JW Infect Dis Jun 2017). However, the optimal time for administration of bezlotoxumab during the course of antibiotic treatment for CDI has been unclear.

A post hoc analysis of two placebo-controlled phase III studies involving 1554 patients, 781 of whom received bezlotoxumab, sheds light on timing. In these studies, 42%, 30%, and 28% of patients received bezlotoxumab or placebo 0 to 2, 3 to 4, and >5 days after initiation of antibacterial treatment for CDI, respectively. Regardless of timing of administration, initial clinical cure rates did not differ between bezlotoxumab and placebo recipients (range, 78%–82%). Similarly, timing of administration to the bezlotoxumab recipients had no effect on time to resolution of diarrhea. Efficacy of bezlotoxumab was independent of timing of administration (adjusted absolute reductions of CDI recurrence with bezlotoxumab vs. placebo were 12.3%–13.1% in the 3 groups; relative reductions were 39%, 38%, and 36% at 0–2, 3–4, and >5 days after initiation of antibiotic treatment, respectively).

COMMENT: If bezlotoxumab is used for prevention of CDI recurrence, there may be flexibility in timing of administration, but it appears reasonable to give it before the end of antibiotic treatment for a CDI episode. This is in line with previous investigations of *C. difficile* toxin B levels during recurrences. However, whether bezlotoxumab, a tapered vancomycin regimen, or fecal microbiota transplantation is the best strategy for prevention of CDI recurrence remains to be determined. Meanwhile, we have to discuss these options with the patients.



CITATION(S): Birch T et al. Efficacy of bezlotoxumab based on timing of administration relative to start of antibacterial therapy for *Clostridium difficile* infection. J Antimicrob Chemother 2018 May 16; [e-pub]. (<https://doi.org/10.1093/jac/dky182>)

Ann Intern Med 2017 Dec 12

Intensive vs. Individualized Type 2 Diabetes Control

Individualized glycemic control is cost-effective and lowers lifetime medication use.

Intensive diabetes control can lead to severe hypoglycemia or excess early mortality (NEJM JW Gen Med Jul 1 2008 and *N Engl J Med* 2008; 358:2545). Individualized treatment for patients with type 2 diabetes changes glycemic control from universally set, intensive management goals (e.g., glycosylated hemoglobin [HbA_{1c}] <7%) to individualized glycemic goals based on factors such as age, life expectancy, comorbidities, complication history, and hypoglycemia risk). Several years ago, the American Diabetes Association endorsed this “patient-centered approach” (NEJM JW Gen Med Aug 15 2012 and *Diabetes Care* 2012; 35:1364).

In this economic analysis of diabetes management, researchers used a U.S. database of type 2 diabetes patients to demonstrate a lifetime cost-savings of >US\$13,000 per person — achieved through lower medication use — with individualized glycemic control compared with intensive control (HbA_{1c} goal, <7%). Individualized glycemic control marginally decreased life-years (decrement of 0.1 life-years, or 36 days) but was balanced by an equivalent increase in quality-adjusted life-years (increase of 0.1 QALYs, or 36 quality-adjusted life-days). Individualized control also raised lifetime risk for diabetes complications (i.e., myocardial infarction, stroke, or amputation) by about 1% each but decreased risk for severe hypoglycemic events by nearly 1%.

COMMENT: This economic analysis places quality-of-life value on reducing medication use for a chronic condition — a somewhat unique strategy that clinicians might not always consider in their management approach. Shifting patients from more-intensive to less-intensive control over their lifetimes can be patient-centered, and I would not be surprised if we begin to see this type of analysis and approach with other chronic disease conditions.

CITATION(S): Laiteerapong N et al. Individualized glycemic control for U.S. adults with type 2 diabetes: A cost-effectiveness analysis. Ann Intern Med 2017 Dec 12; [e-pub]. (<http://dx.doi.org/10.7326/M17-0537>)

JAMA 2018 Jul 10; 320:167

Acupuncture for Joint Pain Associated with Aromatase Inhibitors for Breast Cancer



This nonpharmacologic intervention helped control joint pain.

Aromatase inhibitors (AIs) increase disease-free survival in menopausal women with hormone-receptor-positive breast cancer, but half of such women experience AI-associated musculoskeletal pain that leads to discontinuation of therapy. Does acupuncture reduce joint pain associated with AIs? U.S. investigators at 11 academic sites conducted a blinded trial in which 226 postmenopausal women receiving an AI for early-stage breast cancer who reported pain scores of ≥ 3 (out of 10) were randomized to true acupuncture, sham acupuncture (shallow needling at non-acupuncture points), or waitlist control (no intervention). Both acupuncture groups received 6 weeks of biweekly acupuncture followed by 6 weeks of once-weekly sessions.

Between baseline and 6 weeks, true acupuncture lowered joint-pain scores more than sham acupuncture (rates of clinically significant 2-point reductions in pain scores, 58% vs. 33%; $P=0.02$) or waitlist control (31%; $P=0.01$). At 12-week follow up, recipients of true acupuncture reported less pain than waitlist controls, but no differences compared with sham acupuncture recipients.

COMMENT: Although these investigators do not say whether acupuncture increased adherence to AIs, their elegant study adds to the scientific literature supporting the benefits of this intervention for pain control. Managing chronic pain remains a clinical challenge; thus, health insurance plans are increasingly covering acupuncture. Given the limited benefits and known risks of narcotics, I often encourage patients with chronic pain to consider trying acupuncture.

CITATION(S): Hershman DL et al. Effect of acupuncture vs sham acupuncture or waitlist control on joint pain related to aromatase inhibitors among women with early-stage breast cancer: A randomized clinical trial. JAMA 2018 Jul 10; 320:167. (<https://doi.org/10.1001/jama.2018.8907>)

Ann Intern Med 2018 Jul 10

How Safe Is Hormone Therapy for Transgender Patients?

A large cohort study suggests that estrogen therapy increases risk for venous thromboembolism in male-to-female individuals.

Many transgender individuals request medical treatment — estrogen for male-to-female (MTF) and testosterone for female-to-male (FTM) individuals — so that their physical appearance is aligned with their gender identity. Using data from enrollees in three integrated health systems, U.S. investigators followed 2842 MTF and 2118 FTM adults for a mean of 4.0 and 3.6 years, respectively. Each transgender person was matched to 10 cisgender men and 10 cisgender women.

There was a significantly higher incidence of venous thromboembolism (VTE) among all MTF enrollees than among cisgender men and cisgender women. In contrast, overall rates of ischemic strokes and myocardial infarction were similar among MTF enrollees and the comparison groups. Due to low numbers of cardiovascular events, the evidence was insufficient to make conclusions regarding risks experienced by FTM enrollees. Among MTF enrollees who initiated estrogen therapy, there were substantial increases in



risk for VTE (starting at 2 years of follow-up) and ischemic stroke (starting at 6 years of follow-up). Oral estradiol was the most common estrogen prescribed (mean daily dose, 4 mg).

COMMENT: This study found that oral estrogen elevates risk for venous thromboembolism among MTF transgender individuals. The findings are consistent with a large European study of transgender individuals (*Clin Endocrinol [Oxf]* 1997; 47:337) and with studies of menopausal hormone therapy and oral contraception in general. The mean dose of oral estradiol used was some four times higher than the standard (1 mg) dose used in menopausal therapy. (The authors noted that some patients may have obtained medications from other sources, which could not be accounted for in the analysis.) Further studies are needed to develop best practices with respect to dose and route (oral vs. transdermal) in the hormonal management of transgender individuals.

CITATION(S): Getahun D et al. Cross-sex hormones and acute cardiovascular events in transgender persons: A cohort study. *Ann Intern Med* 2018 Jul 10; [e-pub]. (<https://doi.org/10.7326/M17-2785>)

J Adolesc Health 2018 Jul 5

Risky Driving Behavior Among U.S. Adolescents Before and After Licensure

The rate of crashes or near-crashes among teen drivers rose eightfold after they finished the learner period and began driving independently.

To investigate possible causes for excess crash rates in new adolescent drivers, researchers monitored 90 adolescent drivers while they possessed learner permits and after they were newly licensed, comparing them with 131 experienced adult drivers. Vehicles were equipped with a data acquisition system to capture miles driven and video-record drivers. Crash/near-crash (CNC) and kinematic risky driving (KRD) rates were analyzed with respect to gender, time of day (day/night), and road condition (wet/dry).

CNC and KRD rates of adolescents were similar compared with adult drivers during the teens' learner phase but were eightfold (CNC) and fourfold (KRD) higher during the first quarter of independent driving. During the independent driving phase, adolescent KRD rates were higher for adolescent boys versus adolescent girls and higher than adult rates irrespective of time of day or road condition.

COMMENT: This study underscores the importance of both providers and parents discussing safe driving practices with adolescents, not only while they learn to drive, but also after they are independently licensed. Safe driving during the learner period did not predict the same as an independent driver. Even though there may be initial pushback from adolescents, these findings suggest that continued presence of adults in the car with new drivers after independent licensure could lessen risky driving behaviors. New accelerometer technology is available to assess KRD events, providing immediate feedback to drivers and reports to parents, with proven effectiveness in reducing the KRD rate of new adolescent drivers. However, the benefits of this technology cannot be harnessed when adolescents are offered older, less technologically advanced vehicles. Perhaps the common practice of giving adolescents the old car should be rethought?



CITATION(S): Gershon P et al. Crash risk and risky driving behavior among adolescents during learner and independent driving periods. J Adolesc Health 2018 Jul 5; [e-pub].
(<https://doi.org/10.1016/j.jadohealth.2018.04.012>)

J Pediatr 2018 Jul 6

Parents Commonly Engage in Distracted Driving with Children in the Car

About half of parents talk on the phone; about a third engage in texting.

Distracted driving accounts for thousands of motor vehicle deaths and hundreds of thousands of injuries in the U.S. every year. The use of mobile devices to talk, text, or access the Internet by parents while driving with children in the car not only contributes to these fatalities, but also models that it is acceptable behavior and increases the likelihood that the children who observe it will someday do it, too.

To determine how often parents engage in distracted driving when a child is in the car and what factors are associated with this behavior, researchers conducted an online survey of 760 parents of children aged 4 to 10 years that included questions about mobile device use and other driving-related activities.

While driving with a child in the car, 52% of parents talked on a hands-free phone, 47% talked on a hand-held phone, 34% read text messages, 27% sent text messages, and 14% used social media; there were no race or gender differences in phone-use while driving. Parents with higher incomes were more likely to use a hands-free device and to read or send text messages. Parents who engaged in other unsafe driving practices (such as not always using their child's restraint system) compared with those who did not, were more likely to talk, text, or use social media while driving; these associations were particularly strong for parents who reported driving under the influence of alcohol in the past.

COMMENT: Use of a mobile device while driving — particularly with a child who is not restrained properly — is a potential cause of child motor vehicle mortality and morbidity, but one that is preventable. Pediatric providers should counsel parents to eliminate this behavior for safety reasons, as well as to model setting boundaries around technology and reinforce the idea that no text or social media post is ever worth a car accident.

CITATION(S): McDonald CC et al. Factors associated with cell phone use while driving: A survey of parents and caregivers of children ages 4–10 years. J Pediatr 2018 Jul 6; [e-pub].
(<https://doi.org/10.1016/j.jpeds.2018.06.003>)

